This document is scheduled to be published in the Federal Register on 05/20/2022 and available online at **federalregister.gov/d/2022-10698**, and on **govinfo.gov**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2022-D-0277]

Risk Management Plans To Mitigate the Potential for Drug Shortages; Draft Guidance for Industry; Availability; Agency Information Collection Activities; Proposed Collection; Comment Request

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or we) is announcing the availability of a draft guidance for industry entitled "Risk Management Plans to Mitigate the Potential for Drug Shortages." This draft guidance is intended to help stakeholders develop, maintain, and implement, as appropriate, risk management plans (RMPs) to proactively assist in the prevention of human drug product and biological product shortages. In March 2020, with the enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), the Federal Food, Drug, and Cosmetic Act (FD&C Act) was amended to require certain manufacturers to develop, maintain, and implement, as appropriate, a "redundancy risk management plan." This draft guidance provides information about the development and content of RMPs for those manufacturers as well as for other stakeholders. This draft guidance recommends a framework and factors to consider that stakeholders can use to develop RMPs. This draft guidance is relevant for all stakeholders, including those with oversight and control responsibilities for drug quality and contract establishments, and for manufacturers of active pharmaceutical ingredients (APIs), approved or licensed drug and biological products, and drug products marketed without an application.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance. Submit electronic or written comments on the proposed collection of information in the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF THE PUBLICATION OF THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2022-D-0277 for "Risk Management Plans to Mitigate the Potential for Drug Shortages." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request or include a Fax

number to which the draft guidance may be sent. See the SUPPLEMENTARY INFORMATION section for information on electronic access to the draft guidance.

FOR FURTHER INFORMATION CONTACT:

With regard to the draft guidance: Karen Takahashi, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 75, Rm. 6686, Silver Spring, MD 20993-0002, 301-796-3191; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

With regard to the proposed collection of information: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Risk Management Plans to Mitigate the Potential for Drug Shortages." This draft guidance is intended to help stakeholders[1] develop, maintain, and implement, as appropriate, RMPs to proactively assist in the prevention of human drug product and biological product shortages. In March 2020, with the

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[1] For the purposes of this guidance, the term *stakeholder* includes each manufacturer of a drug described in section 506C(a) of the FD&C Act (21 U.S.C. 356c(a)) or of any API included in such drugs. (See generally section 506C(j) of the FD&C Act.) The term *stakeholder* also broadly includes any person or entity who has oversight and control over the manufacture of drugs to ensure quality or owns or operates an establishment (as defined in 21 CFR 207.1 and 600.3) that manufactures a drug or biological product. Examples of stakeholders include contract facilities as referenced in 21 CFR 200.10(b); applicants with an approved new drug application, abbreviated new drug application, or an approved biologics license application; manufacturers of drug products marketed without an approved application; manufacturers of components, including APIs, intended for use in the manufacture of drug products; and manufacturers of drug-led, drug-device or biologic-led, biologic-device combination products (as defined in 21 CFR 3.2(e)) regulated by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research. This guidance references specific stakeholders individually where appropriate (e.g., if a specific section of the guidance is relevant to specific stakeholders only); otherwise, recommendations that refer to the manufacture of *drugs* are generally relevant to all stakeholders with the roles described above with respect to human drug and biological products.

enactment of the CARES Act (Pub. L. 116-136), Congress added section 506C(j) to the FD&C Act, which requires certain manufacturers to develop, maintain, and implement, as appropriate, a "redundancy risk management plan that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which such drug or active pharmaceutical ingredient of such drug is manufactured." Section 506C(j) of the FD&C Act became effective September 23, 2020. This guidance provides information about the development and content of RMPs for those manufacturers as well as for other stakeholders.

Drug shortages pose a significant public health threat that can delay, and in some cases even deny, critically needed care for patients. FDA views RMPs as an important mechanism for stakeholders to proactively identify, assess, and mitigate the risks that might lead to a disruption in the supply of drug products, thus preemptively reducing the probability of a drug shortage, and preserving the private and public resources used in resolving the shortage.

Based on recent publications and reports, the majority of drug shortages are associated with quality issues. This guidance proposes a framework stakeholders can use to develop RMPs that aligns with principles stated in the International Council for Harmonisation guidance for industry entitled "Q9 Quality Risk Management" (available at https://www.fda.gov/media/71543/download). In addition, FDA also recommends several factors to consider when developing the content of the RMPs. This guidance is relevant for all stakeholders, including those with oversight and control responsibilities for drug quality and contract establishments, and for manufacturers of APIs, approved or licensed drug and biological products, and drug products marketed without an application.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Risk Management Plans to Mitigate the Potential for Drug Shortages." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

II. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, we invite comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Discontinuance or Interruption in the Production of Life-Saving Drugs;

OMB Control Number 0910-0045--Revision

This information collection helps support implementation of requirements under section 506C(j) of the FD&C Act. Section 506C(j) of the FD&C Act *requires* manufacturers of drug products described in section 506C(a) of the FD&C Act or of any active pharmaceutical ingredient or any associated medical devices used for preparation or administration included in the drug to develop, maintain, and implement, as appropriate, a redundancy RMP that identifies and evaluates risks to the supply of the drug, as applicable, for each establishment in which such drug or active pharmaceutical ingredient of such drug is manufactured.

For purposes of this analysis, respondents are those identified in the draft guidance, section III.A., Stakeholders in the Manufacturing Supply Chain. A primary stakeholders is generally the entity that determines which materials and services are necessary to produce a drug product. Secondary stakeholders are entities that are expected to have more detailed insight into specific segments of the supply chain for a drug product but may not have an understanding of its entirety. Finally, other stakeholders, such as inactive ingredient manufacturers, packagers, and distributors, are involved in other segments of the supply chain. In the draft guidance, section IV., RMP Framework and Development Strategy, we discuss specific recommendations regarding the RMP.

We estimate the burden of this collection of information as follows:

Table 1. Estimated Annual Recordkeeping Burden[1]

Section 506C(j) of the FD&C Act; Recordkeeping Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Records	Average Burden per Recordkeeping[2]	Total Hours
Developing an RMP; Guidance for Industry section IV.B.	2,600	1	2,600	29.32 (range 25 to 250)	76,250
Updating an RMP	5,200	1	5,200	2.93 (range 2.5 to 25)	15,250
Total					91,500

[1] There are no capital costs or operating and maintenance costs associated with this information collection.

[2] Figure has been rounded.

We assume a total of 2,600 respondents will incur an initial burden associated with developing an RMP based on recommendations described in the draft guidance. This figure is comprised of 50 primary stakeholders; 1,125 secondary stakeholders; and 1,425 other stakeholders, and represents half the total number of respondents we identify for each of the three respective categories.

For burden associated with updating an RMP, we include all respondents in the respective three categories, for a total of 5,200.

We believe the overall burden for collecting information and preparing RMPs depends on the stakeholder type (primary, secondary, or other stakeholder) and its operation.

We anticipate that stakeholders will be able to leverage information across products, but we understand that the actual burden for a given stakeholder will depend on the portfolio of covered products and the complexity of their operations. Our estimate reflects what we believe is the average burden among all respondents.

This draft guidance also refers to previously approved FDA collections of information found in FDA regulations. The collections of information found in 21 CFR 310.306, 314.81(b)(3)(iii), and 600.82 on notifying FDA of a permanent discontinuance or an interruption in manufacturing of certain drugs or biological products, and 21 CFR part 314 new drug and abbreviated new drug applications, and 21 CFR part 600 biologics license applications have been approved under OMB control numbers 0910-0001 and 0910-0338, respectively; the collections of information in 21 CFR parts 210 and 211 on current good manufacturing practice have been approved under OMB control number 0910-0139.

III. Electronic Access

Persons with access to the internet may obtain an electronic version of the draft guidance at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or https://www.regulations.gov.

Dated: May 13, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2022-10698 Filed: 5/19/2022 8:45 am; Publication Date: 5/20/2022]